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Impaired Insulin Action in Primary Hyperaldosteronism

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Summary

The presence of insulin resistance is frequently found in essential hypertension. There are, however, only sparse data with respect to the potential presence of insulin resistance in patients with secondary hypertension. We have therefore undertaken a study to reveal the potential occurrence of insulin resistance in primary hyperaldosteronism (PH). The hyperinsulinemic euglycemic clamp technique together with the evaluation of insulin receptor characteristics were used to study insulin resistance in 12 patients with PH. The measured parameters were compared to normal values in control subjects. We have found a significantly lower glucose disposal rate (M, μmol/kg/min) (18.7±6 vs. 29.3± 4), decreased tissue insulin sensitivity index (M/I, μmol/kg/min per mU/l x100) (23.7±9.8 vs. 37.5±11.6) and also lower metabolic clearance rate of glucose (MCRg, ml/kg/min) (3.8±1.5 vs. 7.0±1.1) in patients with primary hyperaldosteronism. The insulin receptor characteristics on erythrocytes did not differ in primary hyperaldosteronism as compared to control healthy subjects. We thus conclude that insulin resistance is also present in secondary forms of hypertension (primary hyperaldosteronism) which indicates the heterogeneity of impaired insulin action in patients with arterial hypertension.

Key words

Aldosterone • Insulin • Primary hyperaldosteronism • Insulin resistance

Introduction

Insulin resistance is present in about 50 % of patients with primary hypertension (Reaven *et al.* 1996). The possible relationship between high blood pressure and insulin action has been suggested, but the exact mechanisms whereby insulin action leads to the clinical manifestation of arterial hypertension are not clearly understood (Reaven 1988, Zemel 1995). There are numerous data indicating the possible relationship between altered insulin action and high blood pressure in primary hypertension (for reviews see Shen *et al.* 1988, Reaven *et al.* 1996). However, only sparse data are available concerning the insulin action in secondary hypertension (Natali *et al.* 1996).

Our preliminary results indicated the presence of insulin resistance in patients with primary hyperaldosteronism (Škrha *et al.* 1997). This type of secondary hypertension was chosen because no apparent counterregulatory hormonal systems to insulin action are activated. We have undertaken the present study to evaluate potential changes in insulin action in primary hyperaldosteronism and to assess a possible correlation between plasma aldosterone and insulin sensitivity in this disease.

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Materials and Methods

We have studied 12 patients with primary hyperaldosteronism (mean age 50±13 years, body mass index 28.3±4.8 kg/m^2): five patients with aldosterone-producing adenoma (APA) and seven patients with idiopathic hyperaldosteronism (IHA) due to bilateral hyperplasia. The diagnosis of primary hyperaldosteronism and classification into the subtypes was made on the basis of laboratory (plasma renin, aldosterone, aldosterone/renin ratio, postural, captopril and dexamethasone tests) as well as morphological methods (adrenal CT scan). Blood pressure was measured by mercury sphygmomanometer and by 24-h blood pressure monitoring systems (Spacelab 90207). Although some patients tended to have a borderline body mass index, all subjects revealed normal glucose tolerance confirmed by the oral glucose tolerance test. Antihypertensive therapy was withdrawn at least one week before the study. In order to prevent hypokalemia, all patients were regularly treated by potassium supplements. The control group consisted of 9 healthy subjects of corresponding age and body mass index (BMI).

The hyperinsulinemic euglycemic clamp was performed as follows: all subjects were examined after an overnight fast at 07:00 h in the morning. After cannulation of the forearm vein, blood samples were obtained for determination of insulin, C-peptide, plasma glucose and potassium concentrations. The cannula was then connected with an infusion pump to administer wash-out sodium saline solution (0.9 %), the insulin solution (160 units of HM Actrapid 40, Novo-Nordisk in 500 ml 0.9 % sodium saline) and 40 % glucose solution. At the same time it was connected to a perfusor (Infuser Secura FT, B. Braun, Germany), administering 7.5 % potassium chloride solution. A double-lumen catheter was inserted into the contralateral arm for continuous blood glucose determination by Biostator (GCSII, Elkhart, Indiana, USA) (Albisser *et al.* 1974). After a 30 min washout period, hyperinsulinemic euglycemic clamp was performed by Biostator (mode 7:1) during 120 min at the insulin infusion rate of 1 mU.kg^{-1}.min^{-1} (Fogt *et al.* 1978). Blood glucose established during the clamp was separately confirmed by a glucose analyzer. Blood samples for the determination of biochemical variables were withdrawn from a third cannula inserted into a wrist vein.

Plasma potassium concentrations were maintained at constant level during the clamp. Two blood samples for insulin and C-peptide determination were collected in the last 20 min of the clamp.

The results were used to calculate the following characteristics of insulin action: glucose disposal rate (M, μmol.kg^{-1}.min^{-1}), tissue sensitivity index of insulin (M/I, μmol.kg^{-1}.min^{-1} per mU.l^{-1} x 100) defined as the ratio of glucose disposal rate to insulin concentration, metabolic clearance rate (MCRg, ml.kg^{-1}.min^{-1}). The characteristics of insulin receptors on erythrocytes were evaluated in all subjects. The binding capacity of receptors (B), their number (Ro) and empty site affinity (Ka) were calculated using computer software (Hovorka and Hilgertová 1991).

Plasma potassium, glucose, insulin, C-peptide, aldosterone and renin concentrations were measured by commercial RIA kits (Immunotech, Czech Republic).

The results are presented as means ± SD. T-test was used to compare the two groups of subjects.

Table 1. Clinical and laboratory characteristics of patients with primary hyperaldosteronism (n=12).

Casual blood pressure (SBP/DBP) (mm Hg)	165±35/113±19
Mean 24-h blood pressure (SBP/DBP) (mm Hg)	168±21/103±9
Plasma potassium (mmol/l) *(normal values 3.8-5.2)*	3.9 ± 0.8
Plasma cortisol (nmol/l) *(normal values 180-650)*	380 ± 112
Recumbent plasma renin activity (PRA) (ng/ml/h) *(normal values 0.7-2.6)*	0.20 ± 0.09
Recumbent plasma aldosterone (PA) (pg/ml) *(normal values 30-150)*	470 ± 205
Plasma aldosterone/renin ratio # *(normal values < 30)*	284 ± 162

Results are expressed as means ± S.D. # PA/PRA ratio is calculated from PA values in ng/100 ml and PRA values in ng/ml/h.

Results

Clinical and laboratory characteristics of patients with primary hyperaldosteronism are shown in Table 1. The results clearly confirm the diagnosis of patients with primary hyperaldosteronism (PH) in which blood pressure was elevated. Due to prolonged substitution therapy with potassium supplements the plasma

potassium levels were not markedly reduced but remained at limits of normal values.

The parameters related to insulin action in PH and controls are summarized in Table 2. The insulin resistance was observed in patients with PH who had normal plasma glucose (Go) and insulin (Io) values. We found significantly lower levels of the glucose disposal rate (M) ($p<0.01$), decreased tissue sensitivity index (M/I) ($p<0.02$) and a lower metabolic clearance rate of glucose (MCRg) ($p<0.01$) in subjects with PH compared to the controls. The characteristics of insulin receptors on erythrocytes of PH patients did not differ from those of the controls.

No significant correlation was found between plasma aldosterone concentrations and the tissue sensitivity index to insulin (M/I, r = 0.016, n.s.), or between the M/I index and plasma potassium levels.

Table 2. Parameters of insulin action in primary hyperaldosteronism (PH) and controls (C).

	PH (n=12)	C (n=9)
Go (mmol/l)	5.0±0.6	4.9±0.4
Io (mU/l)	19.5±10	15.3±7.3
M (μmol/kg/min)	18.7±6.3*	29.3±3.7
M/I (μmol/kg/min//mU/l x 100)	23.7±10*	37.5±12
MCRg (ml/kg/min)	3.8±1.5*	7.0±1.1
B (%)	13.9±2	12.8±1.5
Ro (pmol/l)	256±98	288±100
Ka (10^8/mol)	12.9±4.6	13.0±1.9

*Go – basal plasma glucose, Io – basal serum insulin, M – glucose disposal rate in the last 20 min of clamp, M/I – tissue sensitivity index of insulin, MCRg – metabolic clearance rate of glucose, B – insulin receptor binding capacity, Ro – number of receptors, Ka – empty site affinity. * Significantly different ($p<0.05$) from the controls.*

Discussion

The association between arterial hypertension and insulin resistance has long been established. Although approximately 50 % of all patients with essential hypertension have hyperinsulinism (Reaven *et al.* 1996), its role in the pathogenesis of hypertension is poorly understood (Kaplan 1998).

Primary hyperaldosteronism (PH) is a model of secondary hypertension, where no apparent activation of the counterregulatory hormonal systems is noted. Some authors consider PH to be one of the rare causes of diabetes (Natali *et al.* 1996). We did not find any subject with impaired glucose tolerance in our patients with PH. Furthermore, the prevalence of diabetes in our large group of PH patients (n=135) is comparable with the normal population of corresponding age and BMI (unpublished observation).

Our results confirm the presence of insulin resistance in subjects with PH. The absence of differences in receptor characteristics in PH may indicate postreceptor disturbances. The observed insulin resistance may correspond to plasma potassium and/or aldosterone changes. However, this is unlikely because of the lack of correlation between M/I, M or MCRg values and the former parameters. We certainly cannot fully exclude the possibility of hypokalemia-induced changes in vascular tone which may, to some extent, contribute to the insulin resistance. This hypothesis, however, seems to be unlikely with respect to the normokalemia in most subjects at the time of the study.

The possible association between BMI and M/I may also exist in PH, as in other populations (Škrha *et al.* 1996). However, the observed correlation between these two parameters in our study was of borderline significance (r = –0.50, p = 0.06). This could be due to the low number of examined subjects.

Our results are in discordance with another study (Ishimori *et al.* 1994), where insulin sensitivity was increased in patients with an aldosterone-producing adenoma. The different results between these two studies may arise from the different methodology, since Ishimori *et al.* (1994) did not employ the clamp technique and a different population of patients was studied. While the prevailing form of primary hyperaldosteronism in our subjects concerned patients with idiopathic hyperaldosteronism (bilateral hyperplasia), in Ishimori's study only subjects with aldosterone-producing adenoma were studied. At present, we try to extend the two subgroups of patients with primary hyperaldosteronism.

In conclusion, our study demonstrates the presence of insulin resistance in patients with primary hyperaldosteronism, which suggests the heterogeneity of impaired insulin action in arterial hypertension.

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